CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	202-813 (Related IND 101,639)
Submissions Date:	05/24/2011 (SDN 1)
Submission Type:	505(b)(2)
Brand Name:	QNASL
Generic Name:	Beclomethasone Dipropionate (BDP) HFA nasal aerosol
Sponsor:	Teva Respiratory, LLC
Route of Administration:	Intranasal
Dosage Form:	Nasal aerosol spray solution
Dosage Strength:	Each actuation of the aerosol delivers 80 mcg of BDP
OND Division:	Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Arun Agrawal, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
Indication:	Treatment of symptoms of seasonal and perennial allergic rhinitis
Dosage Administration:	Adults and children 12 years of age and over: 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day)

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1.0 EXECUTIVE SUMMARY

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 202-813 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Sponsor markets an approved beclomethasone dipropionate (BDP) HFA oral inhalation aerosol for the treatment of asthma (QVAR®, NDA 20-911), and is seeking approval of a BDP HFA nasal aerosol, utilizing the same chemical formulation and concentration as the QVAR, with a nasal actuator for use by the intranasal route for the treatment of allergic rhinitis (AR). In support of this NDA, data from two clinical pharmacology studies and four clinical studies were submitted. The goals of the clinical pharmacology program were: (i) to compare the systemic exposure of the proposed product following intranasal administration to that from QVAR following oral inhalation (relative bioavailability, study BDP-AR-101), and (ii) to characterize the effects of intranasal administration of the proposed product on hypothalamic-pituitary-adrenal (HPA)-axis function (study BDP-AR-304).

Relative Bioavailability (Study BDP-AR-101): This single dose, randomized, open-label, 3-period, crossover trial in healthy volunteers determined pharmacokinetics of BDP and its active major metabolite beclomethasone 17-monopropionate (17-BMP, it is reported to be mainly responsible for the pharmacological activity following BDP administration) following (a) intranasal administration of BDP HFA at 80 mcg and 320 mcg, and (b) oral inhalation of BDP HFA 320 mcg (QVAR). The AUClast for 320 mcg intranasal aerosol was 27.5% and 12.7% of that of oral inhalation for 17-BMP and BDP, respectively. The Cmax for intranasal aerosol was 19.5% and 6.1% of that of oral inhalation for 17-BMP and BDP, respectively. Overall, systemic exposures of BDP and 17-BMP were much lower following intranasal dosing as compared to oral inhalation at the same dose of 320 mcg.

PK parameters for 17-BMP and BDP

	Geometric LS Mean			320 mcg Intranasal / 320 mcg Orally Inhaled
Parameter	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg Orally Inhaled	Ratio (90% CI)
	17-BMP			
AUClast (hr*pg/mL)	295.827	1139.742	4140.253	0.275 (0.214, 0.354)
Cmax (pg/mL)	92.118	262.654	1343.692	0.195 (0.158, 0.241)
	BDP			
AUClast (hr*pg/mL)	14.584	53.561	422.917	0.127 (0.096, 0.167)
Cmax (pg/mL)	64.379	181.951	2993.101	0.061 (0.047, 0.079)

Effect on HPA Axis Function (Study BDP-AR-304): This repeat-dose, randomized, double-blind, parallel-group trial investigated the effects of BDP HFA nasal aerosol (320 mcg) on the HPA-axis function, as assessed by 24-hour serum cortisol measurements, in adolescent and adult patients with perennial allergic rhinitis (PAR). This trial compared the effects of 6 weeks of daily treatment with BDP HFA nasal aerosol with the effects of 6 weeks of daily treatment with placebo, or with the effects of 7 days of daily treatment with active control prednisone (10 mg once daily) on HPA-axis function. Overall, BDP HFA intranasal treatment did not result in serum cortisol suppression relative to its pretreatment baseline and to the placebo treatment, while the active control prednisone treatment resulted in a substantial reduction in serum cortisol levels.

Summary of serum cortisol (mcg/dL) weighted mean

Statistic	**BDP HFA320 mcg/day N = 48**	**Placebo N = 41**
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.04)	0.95 (1.03)
Ratio of BDP to Placebo	0.96	
95% CI	(0.87, 1.06)	
	Prednisone 10 mg/day N = 9	**Placebo N = 41**
Baseline geometric mean (SE)	7.33 (1.11)	8.45 (1.05)
Week 6 geometric mean (SE)	2.31 (1.20)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.31 (1.14)	0.95 (1.03)
Ratio of Placebo to prednisone 10 mg/day	3.17	
95% CI	(2.68, 3.74)	

Following repeated once-daily administration of 320 mcg BDP HFA nasal aerosol for 6 weeks, the mean AUC_{0-t} for 17-BMP was 1055 hr*pg/mL, the mean AUC_{0-24} was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL. Following 6 weeks of daily treatment, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

Overall, adequate clinical pharmacology information was provided in support of this NDA.

2.0 QUESTION BASED REVIEW

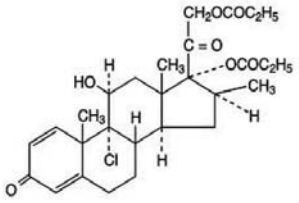
2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

BDP was previously formulated and developed as an aqueous nasal spray (Vancenase AQ, Beconase AQ) for the treatment of AR. Both of these products were also marketed as CFC metered dose inhaler (MDI) nasal aerosols prior to being withdrawn from market with the phase out of CFC-containing nasal products. Sponsor has developed this BDP HFA nasal aerosol, utilizing the same chemical formulation and concentration as their approved orally inhaled BDP HFA formulation (QVAR) for asthma, with a nasal actuator to be used by the intranasal route for the treatment of AR.

2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

BDP is an anti-inflammatory steroid di-ester of beclomethasone and is chemically related to dexamethasone. BDP nasal aerosol is a pressurized, non-aqueous solution in a metered-dose aerosol device intended only for intranasal use. It contains a solution of BDP in HFA propellant and dehydrated ethanol. Chemical structure of BDP is as follows:



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

BDP is a synthetic corticosteroid. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells and the release of inflammatory mediators. In vitro binding affinity of 17-BMP for human glucocorticoid receptor is reportedly 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide, and 25 times that of BDP. BDP HFA is being indicated for the treatment of AR, however, the precise mechanism of its action is not known.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Adults and children 12 years of age and over: 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day).

2.1.5 What is the to-be-marketed formulation?

The to-be-marketed formulation contains a solution of BDP in HFA propellant and dehydrated ethanol.

Formulation Configuration

Ingredient	80 mcg/Actuation (ex-actuator) (% w/w)
Beclomethasone Diproprionate (anhydrous), USP	0.169
Dehydrated Alcohol, USP	(b) (4)
HFA-134a	

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Following two clinical pharmacology studies were submitted in support of this product:

Relative Bioavailability (Study BDP-AR-101): This was a Phase 1, single-center, single-dose, randomized, open-label, 3-period crossover, PK study in male or female healthy volunteers (18-45 years old). This study was designed to evaluate the hypothesis that systemic exposure of intranasally administered BDP would be less as compared to that of approved orally inhaled BDP (QVAR) thus bridging the systemic safety of QVAR to the proposed intranasal BDP HFA nasal aerosol.

Study Treatments

Treatment	Dose/actuation	Dose	Route of administration	Duration of Treatment
A	40 mcg/actuation 1 actuation/nostril	80 mcg/day	Intranasal	Single dose
B	80 mcg/actuation 2 actuations/nostril	320 mcg/day	Intranasal	Single dose
C	80 mcg/actuation 4 inhalations	320 mcg/day	Oral inhalation	Single dose

Treatment C: QVAR 80 mcg oral inhalation aerosol

Pharmacokinetics of 17-BMP: The AUClast and Cmax for BDP HFA nasal aerosol 320 mcg were 27.5% and 19.5% of that of orally inhaled BDP HFA 320 mcg for 17-BMP, respectively. The Tmax was higher (1.0 vs. 0.25 hr), and the t1/2 slightly lower (4.5 vs. 5.0 hr), for nasal aerosol as compared to oral inhalation. Overall, the systemic exposure of 17-BMP following intranasal administration of 320 mcg BDP HFA was approximately $1/4^{th}$ as compared to orally inhaled BDP HFA at 320 mcg dose. The AUClast and Cmax for 80 mcg BDP HFA nasal aerosol were approximately 26% and 35% of that of 320 mcg BDP HFA nasal aerosol for 17-BMP, respectively. The Tmax for both treatment groups was 1.0 hr, and the t1/2 was slightly lower (3.5 vs. 4.5 hr) for 80 mcg dose.

PK parameters for 17-BMP

	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
Parameter	**BDP HFA 80 mcg Intranasal**	**BDP HFA 320 mcg Intranasal**	**BDP HFA 320 mcg orally Inhaled**	**Ratio (90%CI)**	**Ratio (90% CI)**
AUC_{last} (hr*pg/mL)	295.827	1139.742	4140.253	0.275 (0.214, 0.354)	0.071 (0.055, 0.092)
C_{max} (pg/mL)	92.118	262.654	1343.692	0.195 (0.158, 0.241)	0.069 (0.055, 0.085)
$AUC_{0-\infty}$ (hr*pg/mL)	747.116	1661.529	4419.331	0.376 (0.322, 0.439)	0.169 (0.137, 0.209)
t_{max} (hr)[1]	1.000	1.000	0.250	0.750 [2] (0.459, 0.834) [2]	0.750 [2] (0.417, 0.834) [2]
$t_{1/2}$ (hr)[3]	3.541 (1.2076)	4.457 (1.5899)	5.017 (1.3825)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.1, Table 5 and Table 6
[1] The values represent the median t_{max} for each treatment.
[2] The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.
[3] The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Pharmacokinetics of BDP: The AUClast and Cmax for BDP HFA nasal aerosol 320 mcg were 12.7% and 6.1% of that of orally inhaled BDP 320 mcg for BDP, respectively. The Tmax and t1/2 were similar for both the treatments. The AUClast and Cmax for 80 mcg BDP HFA nasal aerosol were 27.2% and 35.4% of that of 320 mcg BDP HFA nasal aerosol for BDP, respectively. The Tmax and t1/2 were similar for both the treatments.

PK parameters for BDP

	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
Parameter	**BDP HFA 80 mcg Intranasal**	**BDP HFA 320 mcg Intranasal**	**BDP HFA 320 mcg Orally Inhaled**	**Ratio (90%CI)**	**Ratio (90% CI)**
AUC_{last} (hr*pg/mL)	14.584	53.561	422.917	0.127 (0.096, 0.167)	0.034 (0.026, 0.046)
C_{max} (pg/mL)	64.379	181.951	2993.101	0.061 (0.047, 0.079)	0.022 (0.017, 0.028)
$AUC_{0-\infty}$ (hr*pg/mL)	27.160	88.227	434.510	0.203 (0.165, 0.250)	0.063 (0.036, 0.108)
t_{max} (hr)[1]	0.083	0.083	0.083	0.000[2] (0.000, 0.000)[2]	0.000[2] (0.000, 0.000)[2]
$t_{1/2}$ (hr)[3]	0.306 (0.1374)	0.278 (0.1434)	0.313 (0.2455)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.2, Table 8 and Table 9
[1] The values represent the median t_{max} for each treatment.
[2] The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.
[3] The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Overall, BDP HFA nasal aerosol (320 mcg) exhibited considerably lower systemic exposure of BDP and 17-BMP as compared to that of orally inhaled BDP 320 mcg dose.

Effect on HPA-Axis Function (Study BDP-AR-304): This was a randomized, double-blind, placebo- and active-controlled (prednisone 10 mg/day), parallel-group, 6-week study to investigate the effect of BDP HFA nasal aerosol on the HPA-axis when administered to subjects 12-45 years of age with PAR.

Subjects were randomly assigned in a 4:4:1 ratio to receive BDP HFA nasal aerosol 320 mcg/day, placebo nasal aerosol, or placebo nasal aerosol plus prednisone 10 mg/day. Subjects self administered the double-blinded nasal aerosol (BDP HFA nasal aerosol or placebo) once daily in the morning as 2 actuations per nostril for 6 weeks and also took a double-blind capsule (prednisone 10 mg or placebo) once daily during the last 7 days of treatment. At the end of treatment, subjects were domiciled for PD measurements of HPA-axis function and PK measurements for BDP and 17-BMP.

The serum cortisol weighted mean (0-24 hr) at baseline and at week 6, and the ratio of week 6 over baseline were calculated. Geometric mean serum cortisol weighted mean values were similar in the BDP HFA 320 mcg/day and placebo treatment groups at baseline and after 6 weeks of treatment. The ratio of week 6/baseline was 0.90 for BDP HFA 320 mcg/day and 0.95 for placebo. The geometric mean ratio for BDP HFA 320 mcg/day to placebo was 0.96. The ratio of week 6/baseline was 0.31 for the prednisone active treatment. The geometric mean ratio for placebo to prednisone group was 3.17, indicating that prednisone resulted in approximately three-fold reduction in serum cortisol levels compared with placebo alone.

Summary of analyses of logarithmically-transformed serum cortisol (mcg/dL) weighted mean

Statistic	BDP HFA320 mcg/day N = 48	Placebo N = 41
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.04)	0.95 (1.03)
Ratio of BDP to Placebo	0.96	
95% CI	(0.87, 1.06)	
	Prednisone 10 mg/day N = 9	**Placebo N = 41**
Baseline geometric mean (SE)	7.33 (1.11)	8.45 (1.05)
Week 6 geometric mean (SE)	2.31 (1.20)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.31 (1.14)	0.95 (1.03)
Ratio of Placebo to prednisone 10 mg/day	3.17	
95% CI	(2.68, 3.74)	

Source: **Section 5.3.4.2, Study BDP-AR-304, Section 11.4.1, Table 12** and **Table 13**
Serum cortisol values below the limit of quantitation were imputed as the lower limit of quantitation/2 (0.5 mcg/dL)
Results from ANCOVA model including effects for treatment, center, and logarithmically transformed Baseline serum cortisol weighted mean as covariate.

Following repeated once-daily administration of 320 mcg BDP HFA nasal aerosol for 6 weeks, the mean AUC_{0-t} for 17-BMP was 1055 hr*pg/mL, the mean AUC_{0-24} was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL. Following daily treatment for 6 weeks, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

Overall, this study demonstrated that intranasal BDP HFA 320 mcg/day was not associated with suppression of serum cortisol levels in subjects ≥12 years of age with PAR.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

BDP and 17-BMP were measured in plasma (details provided in Appendices). This is a locally (nasal) acting product and therefore, no exposure response relationship was evaluated.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

Sponsor conducted following four clinical efficacy and safety studies:

BDP-AR-201	Phase 2 dose range study in SAR, 2 wks	Efficacy, safety
BDP-AR-301	Pivotal study in SAR patients, 2 wks	Efficacy, safety
BDP-AR-302	Pivotal study in PAR patients, 6 wks	Efficacy, safety
BDP-AR-303	Long term safety study in PAR, 52 wks	Efficacy, safety

Study BDP-AR-201 was a double-blind, randomized, placebo-controlled, parallel-group, multi-center, dose ranging study. The primary objective of this study was to determine the optimally safe and effective dose of BDP HFA nasal aerosol in subjects with SAR. Patients received 3 doses of BDP HFA nasal aerosol (80, 160, and 320 mcg) and placebo daily for 2 weeks. The primary efficacy endpoint was the average AM and PM subject-reported reflective TNSS (rTNSS) over the 2-week treatment period. The LS mean difference between BDP HFA nasal aerosol treatment was -0.63, -0.29, and -0.29 for 320 mcg/day, 160 mcg/day, and 80 mcg/day, respectively. Thus, the largest effect size was obtained with 320 mcg/day treatment. Based on the results of this study, a daily dose of 320 mcg was identified as the optimally safe and effective dose for Phase 3 studies. Study BDP-AR-301 was a two week pivotal efficacy and safety study in SAR patients, study BDP-AR-302 was a six week pivotal efficacy and safety study in PAR patients, while study BDP-AR-301 was a 52 week long term safety study in PAR patients. Please refer to clinical review by Dr. Xu Wang for final assessment of efficacy and safety findings in these four clinical studies.

2.2.4 Exposure Response

No formal PK/PD studies were conducted to establish the relationship between exposure and response as this is a locally (nasal) acting product and systemic exposures will not be an indicator of local efficacy and safety.

2.2.5 Does this drug prolong the QT or QTc interval?

No formal QTc study was conducted.

2.2.6 What are the general PK characteristics of the drug and its major metabolite?

No distribution, metabolism, or elimination studies were performed for BDP HFA nasal aerosol. Following information is provided from the current NDA and previously approved BDP products such as QVAR and Beconase AQ.

2.2.6.1 What are the single dose PK parameters?

The systemic exposure and Cmax of 17-BMP for 80 mcg BDP HFA nasal aerosol dose was 26% and 35.1% of that of 320 mcg dose, respectively. The Tmax for both treatment groups was 1.0 hr; while the t1/2 was slightly lower (3.5 vs. 4.5 hr) for 80 mcg dose as compared to 320 mcg dose. The systemic exposure and Cmax of BDP for 80 mcg BDP dose was 27.2% and 35.4% of that of 320 mcg BDP dose, respectively. The Tmax and t1/2 were similar for both the doses.

PK parameters for 17-BMP and BDP

	Geometric LS Mean		80 mcg Intranasal / 320 mcg Intranasal
Parameter	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	Ratio (90% CI)
	17-BMP		
AUClast (hr*pg/mL)	295.827	1139.742	0.260 (0.201, 0.335)
Cmax (pg/mL)	92.118	262.654	0.351 (0.284, 0.434)
Tmax (hr)	1	1	0.000 (0.000, 0.250)
T1/2 (hr)	3.541	4.457	
	BDP		
AUClast (hr*pg/mL)	14.584	53.561	0.272 (0.205, 0.361)
Cmax (pg/mL)	64.379	181.951	0.354 (0.272, 0.460)
Tmax (hr)	0.083	0.083	0.000 (0.000, 0.000)
T1/2 (hr)	0.306	0.278	

2.2.6.2 What are the multiple dose PK parameters following daily 6 weeks of dosing?

The multiple dose PK of 320 mcg BDP HFA nasal aerosol was evaluated in a randomized, double-blind trial investigating the effects of BDP HFA nasal aerosol on the HPA axis function in adolescent and adult patients with perennial allergic rhinitis. The mean AUC_{0-t} for 17-BMP was 1055 hr*pg/mL, the mean AUC_{0-24} was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL. Following repeated once-daily dosing for 6 weeks, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

2.2.6.3 What are the characteristics of drug absorption?

Most of the BDP undergoes extensive conversion to its active metabolite, 17-BMP, during absorption. Tmax for BDP was approximately 5 minutes after intranasal administration of 320 mcg dose indicating rapid absorption while the Tmax for 17-BMP was 1.0 hr. AUCs for BDP and 17-BMP increased in a dose dependent manner between 80 and 320 mcg doses. Further, this study also showed that the systemic bioavailability of BDP HFA nasal aerosol 320 mcg, as measured by levels of 17-BMP, was approximately four-fold lower than that of orally inhaled BDP HFA 320 mcg (QVAR).

2.2.6.4 What are the characteristics of drug distribution?
Protein binding for 17-BMP was reported to be 94-96% over the concentration range of 1000 to 5000 pg/mL. Vdss for BDP was moderate (20 L) but more extensive for 17-BMP (424 L).

2.2.6.5 What are the characteristics of drug metabolism?
BDP undergoes extensive metabolism via CYP3A4 to form 3 metabolites: 17-BMP, 21-BMP and beclomethasone (BOH). 17-BMP is the major and most active metabolite.

2.2.6.6 What are the characteristics of drug elimination?
The t1/2 of BDP and 17-BMP following intranasal dosing of 320 mcg BDP HFA nasal aerosol were approximately 0.3 hr and 4.5 hr, respectively. Irrespective of the route of administration (injection, oral or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10% of the parent drug and its metabolites are excreted in urine. Intranasal BDP is expected to follow a similar elimination pathway once systemically available.

2.2.6.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
Plasma levels of BDP and 17-BMP increased in a dose dependent manner following a single dose of BDP HFA nasal aerosol at 80 mcg and 320 mcg in healthy volunteers.

2.2.6.8 How do the PK parameters change with time following chronic dosing?
Following repeated once-daily dosing for 6 weeks, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?
No formal PK studies were performed with the BDP HFA nasal aerosol in any special population.

2.3.1.1 Pediatrics
Sponsor is currently seeking approval for ≥12 year old AR patients and has requested a deferral for patients 2-11 years of age. Further, sponsor is seeking waiver of AR studies in children <2 years of age (b) (4) These issues were discussed and agreed on at the pre-NDA meeting between the sponsor and the Division (meeting date 10/18/2010, meeting minutes 11/05/2010). Following is a list of sponsor proposed studies:

(b) (4)		
	Pediatric study in SAR pts 6-11 yrs, 2 wks	Efficacy, safety
	Pediatric study in PAR pts 6-11 yrs, 12 wks	Efficacy, safety
	Pediatric HPA Axis study in children 6-11 yrs, 6 wks	Safety
	Pediatric safety study in PAR pts 2-5 yrs, 12 wks	Safety
	Pediatric HPA Axis study in children 2-5 yrs, 6 wks	Safety

This application was discussed at the PeRC meeting on 01/25/2012. A waiver for studies in pediatric patients less than 2 years of age is justified because of local (nasal) safety concerns with the use of corticosteroids via nasal inhalation in children less than 2 years of age. In addition, appropriate alternatives to corticosteroid nasal sprays exist for use in children less than 2 years of age. A deferral of studies in patients 2 years to less than 12 years of age is appropriate because the product is ready for approval in the older age group. Sponsor is not planning on conducting long-term growth studies with the new product and plans to relay on existing data with QVAR.

PeRC agreed with the waiver for studies in patients birth to less than 2 years of age, and with the plan and assessment for 2-11 year olds.

2.3.1.2 Geriatrics

Clinical studies of BDP HFA nasal aerosol did not include sufficient number of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, administration to elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

2.3.1.3 Renal Impairment

No formal studies were conducted to assess the impact of renal impairment on PK.

2.3.1.4 Hepatic Impairment

No formal studies were conducted to assess the impact of hepatic impairment on PK.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of other drugs, herbal products, diet, smoking, and alcohol use were not evaluated in this submission.

2.4.2 Drug-drug interactions

No formal drug interaction studies were conducted for BDP HFA nasal aerosol.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the BA of the drug from the dosage form?

Not applicable as this is a nasal aerosol spray product.

2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

The to-be marketed formulation was used in the pharmacokinetic and clinical trials.

2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as this is a nasal aerosol spray product.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

LC-MS/MS methods used to determine BDP and 17-BMP in human plasma met the validation acceptance criteria for selectivity/specificity, linearity, precision and accuracy, sensitivity, recovery, dilution integrity, and stabilities. The validated calibration curve ranges were 10-2500 pg/mL for BDP and 20-5000 pg/mL for 17-BMP. Cortisol was quantified by LC-MS/MS (b) (4). Additional analytical details are provided in Appendices.

3.0 DETAILED LABELING RECOMMENDATIONS

Below are some sections from the proposed label. Reviewer suggested changes: ~~double strikethrough~~ text should be deleted from labeling and <u>double underlined</u> text should be added to labeling.

(b) (4)

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Individual Study Synopses:

4.2.1 Relative Bioavailability (Study BDP-AR-101): This was a Phase 1, single-center, single-dose, randomized, open-label, 3-period crossover, PK study in male or female healthy volunteers (18-45 years old). This study was designed to evaluate the hypothesis that systemic exposure of intranasally administered BDP would be less as compared to that of approved orally inhaled BDP (QVAR) thus bridging the systemic safety of QVAR to the proposed intranasal BDP HFA nasal aerosol.

Study Treatments

Treatment	Dose/actuation	Dose	Route of administration	Duration of Treatment
A	40 mcg/actuation 1 actuation/nostril	80 mcg/day	Intranasal	Single dose
B	80 mcg/actuation 2 actuations/nostril	320 mcg/day	Intranasal	Single dose
C	80 mcg/actuation 4 inhalations	320 mcg/day	Oral inhalation	Single dose

Treatment C: QVAR

Pharmacokinetics of 17-BMP: The AUClast and Cmax for BDP HFA nasal aerosol 320 mcg were 27.5% and 19.5% of that of orally inhaled BDP HFA 320 mcg for 17-BMP, respectively. The Tmax was higher (1.0 vs. 0.25 hr), and the t1/2 slightly lower (4.5 vs. 5.0 hr), for nasal aerosol as compared to oral inhalation. Overall, the systemic exposure of 17-BMP following intranasal administration of 320 mcg BDP HFA was approximately 1/4th as compared to orally inhaled BDP HFA at 320 mcg dose. The AUClast and Cmax for 80 mcg BDP HFA nasal aerosol were approximately 26% and 35% of that of 320 mcg BDP HFA nasal aerosol for 17-BMP, respectively. The Tmax for both treatment groups was 1.0 hr, and the t1/2 was slightly lower (3.5 vs. 4.5 hr) for 80 mcg dose.

	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
Parameter	BDP HFA 80 mcg Intranasal	BDP HFA 320 mcg Intranasal	BDP HFA 320 mcg orally Inhaled	Ratio (90%CI)	Ratio (90% CI)
AUC_{last} (hr*pg/mL)	295.827	1139.742	4140.253	0.275 (0.214, 0.354)	0.071 (0.055, 0.092)
C_{max} (pg/mL)	92.118	262.654	1343.692	0.195 (0.158, 0.241)	0.069 (0.055, 0.085)
$AUC_{0-\infty}$ (hr*pg/mL)	747.116	1661.529	4419.331	0.376 (0.322, 0.439)	0.169 (0.137, 0.209)
t_{max} (hr)[1]	1.000	1.000	0.250	0.750 [2] (0.459, 0.834) [2]	0.750 [2] (0.417, 0.834) [2]
$t_{1/2}$ (hr)[3]	3.541 (1.2076)	4.457 (1.5899)	5.017 (1.3825)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.1, Table 5 and Table 6

[1] The values represent the median t_{max} for each treatment.

[2] The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.

[3] The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Pharmacokinetics of BDP: The AUClast and Cmax for BDP HFA nasal aerosol 320 mcg were 12.7% and 6.1% of that of orally inhaled BDP 320 mcg, respectively. The Tmax and t1/2 were similar for both the treatments. The AUClast and Cmax for 80 mcg BDP HFA nasal aerosol were 27.2% and 35.4% of that of 320 mcg BDP HFA nasal aerosol, respectively. The Tmax and t1/2 were similar for both the treatments.

	Geometric LS Mean			320 mcg Intranasal/ 320 mcg Orally Inhaled	80 mcg Intranasal/ 320 mcg Orally Inhaled
Parameter	**BDP HFA 80 mcg Intranasal**	**BDP HFA 320 mcg Intranasal**	**BDP HFA 320 mcg Orally Inhaled**	**Ratio (90%CI)**	**Ratio (90% CI)**
AUC_{last} (hr*pg/mL)	14.584	53.561	422.917	0.127 (0.096, 0.167)	0.034 (0.026, 0.046)
C_{max} (pg/mL)	64.379	181.951	2993.101	0.061 (0.047, 0.079)	0.022 (0.017, 0.028)
$AUC_{0-\infty}$ (hr*pg/mL)	27.160	88.227	434.510	0.203 (0.165, 0.250)	0.063 (0.036, 0.108)
t_{max} (hr)[1]	0.083	0.083	0.083	0.000[2] (0.000, 0.000)[2]	0.000[2] (0.000, 0.000)[2]
$t_{1/2}$ (hr)[3]	0.306 (0.1374)	0.278 (0.1434)	0.313 (0.2455)	---	---

Source: Section 5.3.3.1, Study BDP-AR-101, Section 11.4.1.2, Table 8 and Table 9

[1] The values represent the median t_{max} for each treatment.

[2] The values represent the median treatment difference and the associated 90% confidence interval for the median treatment difference.

[3] The values represent the harmonic mean and the associated jackknife SD in parentheses for each treatment.

Overall, BDP HFA 320 mcg nasal aerosol exhibited considerably lower systemic exposure of BDP and 17-BMP as compared to that of orally inhaled BDP HFA 320 mcg (QVAR) dose.

Bionanlytical Details:

Sample Analysis Summary for Beclomethasone Dipropionate and Beclomethasone 17-Propionate

Report Title	Sample Analysis Report in Support of the Study Entitled, "A Randomized, Open-Label, 3-Period Crossover Study to Investigate the Pharmacokinetics, Safety and Tolerability of BDP HFA Nasal Aerosol in Healthy Volunteers"
Report Number	RPT02256
Analytes	Beclomethasone Dipropionate and Beclomethasone 17-Propionate
Internal Standards (IS)	Beclomethasone Dipropionate-d_{10} for BDP and Beclomethasone 17-Propionate-d_5 for 17-BMP
Sample Receipt Dates (Quantity Received)	3/31/2009 (510 samples, collected on 3/18-29/2009) 4/14/2009 (459 samples, collected on 3/28-4/12/2009) 4/28/2009 (493 samples, collected on 4/8-26/2009) 6/30/2009 (1462 samples, back-up)
Storage Conditions Upon Receipt	Approximately -70 °C
LC-MS/MS Method	RPT02138
Stability History of Samples	61 Days at ~ -70 °C
Matrix/Anticoagulant	Plasma/ K_2 EDTA
Sample Size	0.5 mL of human plasma
Sample Extraction Date Range	April 7, 2009 – May 11, 2009
Extraction Method	Solid phase extraction
Precursor→Product Ion Pairs	521.3→319.3 for Beclomethasone Dipropionate 465.4→279.3 for Beclomethasone 17-Propionate 531.3→319.3 for Beclomethasone Dipropionate-d_{10} 470.4→279.3 for Beclomethasone 17-Propionate-d_5
Standard Curve Range	10-2500 pg/mL for Beclomethasone Dipropionate 20-5000 pg/mL for Beclomethasone 17-Propionate
R-Squared (Mean)	0.9924 for Beclomethasone Dipropionate 0.9931 for Beclomethasone 17-Propionate
Standards Rejected from Linear Regression	36 for Beclomethasone Dipropionate 25 for Beclomethasone 17-Propionate
QC Sample Range	30-2000 pg/mL for Beclomethasone Dipropionate 60-4000 pg/mL for Beclomethasone 17-Propionate
QC Inter-Day Precision (%CV) QCL, QCM, QCH (Mean)	11.78, 6.70, 10.35 for Beclomethasone Dipropionate 9.29, 8.16, 7.22 for Beclomethasone 17-Propionate
QC Inter-Day Accuracy (%RE) QCL, QCM, QCH (Mean)	1.33, -2.70, -1.00 for Beclomethasone Dipropionate 0.50, 0.50, -2.00 for Beclomethasone 17-Propionate

4.2.2 Effect on HPA-Axis Function (Study BDP-AR-304):

This was a randomized, double-blind, placebo- and active-controlled (prednisone 10 mg/day), parallel-group, 6-week study to investigate the effect of BDP HFA nasal aerosol on the HPA-axis function when administered in subjects 12-45 years of age with PAR

Subjects were randomly assigned in a 4:4:1 ratio to receive BDP HFA nasal aerosol 320 mcg/day, placebo nasal aerosol, or placebo nasal aerosol plus prednisone 10 mg/day. Subjects self administered the double-blinded nasal aerosol (BDP HFA nasal aerosol or placebo) once daily in the morning as 2 actuations per nostril for 6 weeks and also took a double-blind capsule (prednisone 10 mg or placebo) once daily during the last 7 days of treatment. At the end of treatment subjects were domiciled for PD measurements of HPA-axis function and PK measurements of BDP and 17-BMP. The serum cortisol weighted mean (0-24 hours) at baseline and at week 6 and the ratio of week 6 over baseline was calculated. Further, pharmacokinetics of 17-BMP and BDP were determined after 6 weeks of treatment with BDP HFA 320 mcg/day.

Effect on HPA-Axis Function: Geometric mean serum cortisol weighted mean values were similar in the BDP HFA 320 mcg/day and placebo treatment groups at baseline and after 6 weeks of treatment. The ratio of week 6/baseline was 0.90 for BDP HFA 320 mcg/day and 0.95 for placebo. The geometric mean ratio for BDP HFA 320 mcg/day to placebo was 0.96. The ratio of week 6/baseline was 0.31 for the prednisone group. The geometric mean ratio for placebo to prednisone group was 3.17, indicating that prednisone resulted in approximately three-fold reduction in serum cortisol levels compared with placebo treatment.

Summary of analyses of logarithmically-transformed serum cortisol (mcg/dL) weighted mean

Statistic	**BDP HFA320 mcg/day N = 48**	**Placebo N = 41**
Baseline geometric mean (SE)	9.04 (1.07)	8.45 (1.05)
Week 6 geometric mean (SE)	8.18 (1.06)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.90 (1.04)	0.95 (1.03)
Ratio of BDP to Placebo	0.96	
95% CI	(0.87, 1.06)	
	Prednisone 10 mg/day N = 9	**Placebo N = 41**
Baseline geometric mean (SE)	7.33 (1.11)	8.45 (1.05)
Week 6 geometric mean (SE)	2.31 (1.20)	8.01 (1.04)
Week 6/Baseline geometric mean ratio (SE)	0.31 (1.14)	0.95 (1.03)
Ratio of Placebo to prednisone 10 mg/day	3.17	
95% CI	(2.68, 3.74)	

Source: **Section 5.3.4.2, Study BDP-AR-304, Section 11.4.1, Table 12** and **Table 13**
Serum cortisol values below the limit of quantitation were imputed as the lower limit of quantitation/2 (0.5 mcg/dL)
Results from ANCOVA model including effects for treatment, center, and logarithmically transformed Baseline serum cortisol weighted mean as covariate.

Pharmacokinetics: The mean AUC_{0-t} for 17-BMP was 1055 hr*pg/mL, the mean AUC_{0-24} was 1214 hr*pg/mL, and the mean C_{max} was 196.9 pg/mL. Following repeated once-daily dosing for 6 weeks, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

Overall, this study demonstrated that BDP HFA 320 mcg/day was not associated with HPA-axis effect in subjects ≥12 years of age with PAR. Cross study comparison with data from study BDP-AR-101 indicates that following repeated once-daily administration of 320 mcg BDP HFA nasal aerosol for 6 weeks, there was no accumulation or increase in plasma exposure of 17-BMP or BDP, most likely due to the short plasma half-life relative to the dosing frequency.

Bionanlytical details

Table 1 Sample analysis summary for beclomethasone dipropionate and beclomethasone 17-propionate

Report Title	Sample Analysis Report in Support of the Study Entitled, "A Randomized, Double-Blind, Placebo- and Active- Controlled, Parallel-Group, 6-Week Study Designed to Investigate the Effects of BDP HFA Nasal Aerosol on the Hypothalamic-Pituitary-Adrenal (HPA)-Axis when Administered in Adolescent and Adult Subjects (12 to 45 Years of Age) with Perennial Allergic Rhinitis (PAR)"
Report Number	RPT02532
Reference Standards	Beclomethasone Dipropionate and Beclomethasone 17-Propionate
Internal Standard (IS)	Beclomethasone Dipropionate-d10 and Beclomethasone 17-Propionate-d5
Sample Receipt Dates	3337 samples (1667 primary and 1670 back-up) were received between 8/4/10 and 9/9/10
Storage Conditions Upon Receipt	-70°C
LC-MS/MS Method	XBL08054-M02
Validated Storage Stability	up to 61 days at -70°C
Species/Matrix/Anticoagulant	human/plasma/K2-EDTA
Sample Size	0.5 mL
Sample Extraction Date Range	8/16/10 to 9/29/10
Extraction Method	Solid phase extraction
Precursor→Product Ion Pairs	521.3→337.3 for Beclomethasone Dipropionate 465.4→279.3 for Beclomethasone 17-Propionate 531.3→319.3 for Beclomethasone Dipropionate-d10 470.4→279.3 for Beclomethasone 17-Propionate-d5
Calibration Curve Range	10 pg/mL to 2500 pg/mL for Beclomethasone Dipropionate 20 pg/mL to 5000 pg/mL for Beclomethasone 17-Propionate
R-Squared (Mean)	0.9942 for Beclomethasone Dipropionate 0.9941 for Beclomethasone 17-Propionate
Standards Rejected from Linear Regression	32 for Beclomethasone Dipropionate 15 for Beclomethasone 17-Propionate
QC Sample Range	30 pg/mL to 2000 pg/mL for Beclomethasone Dipropionate 60 pg/mL to 4000 pg/mL for Beclomethasone 17-Propionate
QC Inter-Day Precision (%CV) QCL, QCM, QCH	13.22, 7.71, 6.82 for Beclomethasone Dipropionate 10.60, 5.83, 4.20 for Beclomethasone 17-Propionate
QC Inter-Day Accuracy (%RE) QCL, QCM, QCH	5.67, -3.30, -2.50 for Beclomethasone Dipropionate 2.17, -4.00, -3.00 for Beclomethasone 17-Propionate

Filing/Survey Form

	Information		Information
NDA Number	**202-813**	**Brand Name**	**QNASL**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Beclomethasone Dipropionate (BDP) HFA Nasal Aerosol**
Medical Division	**DPARP**	**Drug Class**	**Corticosteroid (allergy medicine)**
OCP Reviewer	**Arun Agrawal, Ph.D.**	**Indication(s)**	**BDP HFA nasal aerosol is a corticosteroid indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in adults and adolescent patients 12 years of age and older.**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**BDP HFA nasal aerosol is a non-aqueous nasal spray solution.**
Pharmacometrics Reviewer		**Dosing Regimen**	**The recommended dose of BDP HFA nasal aerosol is 320 mcg per day administered as 2 nasal aerosol sprays in each nostril once daily (maximum total daily dose of 4 nasal aerosol sprays per day).**
Date of Submission	**May 24, 2011**	**Route of Administration**	**Intranasal**
Estimated Due Date of OCP Review	**Feb 17, 2012**	**Sponsor**	**Teva Respiratory, LLC**
Medical Division Due Date	**Feb 17, 2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**March 24, 2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**3**	**3**	**Two PK studies, 1 bioanalytical method validation and 2 bioanalytical reports**
Tabular Listing of All Human Studies	**X**	**2**	**2**	
HPK Summary	**X**	**2**	**2**	
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	**RPT02138 (validation), XLB RPT02256 (Study BDP-AR-101), XLB RPT02532, (Study BDP-AR 304)**
I. Clinical Pharmacology	**X**	**2**	**2**	
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**2**	**2**	
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	**Study # BDP-AR-101**
multiple dose:				
Patients-				
single dose:				

multiple dose:	**X**	**1**	**1**	**Study # BDP-AR-304**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**1**	**Study # BDP-AR-101**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**1**	**1**	**HPA Axis effect, Study # BDP-AR-304**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	**X**	**1**	**1**	
solution as reference:				
alternate formulation as reference:	**X**	**1**	**1**	**Study # BDP-AR-101: alternate route of dosing (inhalation vs. intranasal)**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Waiver requested for 0-<2 year old, Deferral requested for 2-11 year old**
Literature References	**X**			
Total Number of Studies	**X**	**3**	**3**	**Two PK studies, 1 bioanalytical method validation and 2 bioanalytical reports**

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/s/

ARUN AGRAWAL
02/14/2012

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02/14/2012